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(54) Title: 1'-AMINOSPIRO[ISOQUINOLINE-4(1H),3'-PYRROLIDINE]-1,2',3,5'(2H)-TETRONES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS

(57) Abstract

This invention relates to 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones and their pharmaceutically acceptable salts thereof, to processes for their preparation, to methods for using the compounds, and to pharmaceutical preparations thereof. The compounds have pharmaceutical properties which render them beneficial for the prevention or treatment of diabetes mellitus associated complications.

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+ DESIGNATIONS OF "SU"

Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

1'-AMINOSPIRO[ISOQUINOLINE-4(1H),3'-PYRROLIDINE]-1,2',3,5'(2H)-TETRONES AND ANALOGS THEREOF USEFUL AS ALDOSE REDUCTASE INHIBITORS

Background of the Invention

This invention relates to 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones and their pharmaceutically acceptable salts thereof, to processes for their preparation, to methods for using the compounds, and to pharmaceutical preparations thereof. The compounds have pharmaceutical properties which render them beneficial for the prevention or treatment of complications associated with diabetes mellitus.

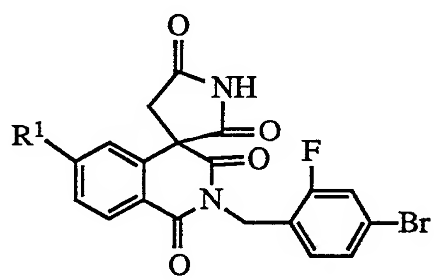
The use of insulin and/or oral hypoglycemic agents in the treatment of diabetes mellitus has prolonged the life of many of these patients. However, their use has not had a demonstrable impact on the development of diabetic complications such as neuropathy, nephropathy, retinopathy, cataracts and vascular disease which accompany the underlying metabolic disorder. There is little question that chronic hyperglycemia plays a major role in the genesis of these complications, and that complete normalization of blood glucose would likely prevent most if not all complications. For a number of reasons, though, chronic normalization of blood glucose has not been achieved with the currently available therapies.

The long-term complications of diabetes develop in tissues where glucose uptake is independent of insulin. In these tissues, which include the lens, retina, kidney and peripheral nerves, the systemic hyperglycemia of diabetes is rapidly transposed into high tissular concentrations of glucose. In all of these tissues this excess glucose is rapidly metabolized by the sorbitol pathway. The intense diabetes-induced flux of glucose through this pathway appears to initiate a cascade of biochemical alterations which slowly progress to cell dysfunction and structural damage. Aldose reductase, the key enzyme in the sorbitol pathway, reduces glucose to sorbitol at the expense of the cofactor NADPH. In animal models of diabetes, compounds which inhibit aldose reductase have been shown to prevent the biochemical, functional and morphological changes induced by hyperglycemia. Early studies by J. H. Kinoshita and collaborators implicated aldose reductase in the etiology of diabetic cataracts. More recent studies have provided compelling evidence that aldose reductase also plays a significant role in the initiation of diabetic nephropathy,

retinopathy and neuropathy (cf McCaleb et al, J. Diab. Comp., *2,* 16, 1989; Robison et al, Invest. Ophthalmol. Vis. Sci., *30,*, 2285, 1989; Notvest and Inserra, Diabetes, *36,* 500, 1987.

Prior Art

The closest prior art is Malamas U.S. Patent 4,927,831, May 22, 1990, which discloses the spiro-isoquinoline-pyrrolidine tetrones of formula

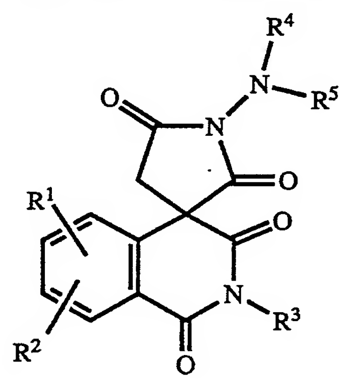


(R^1 is hydrogen or fluorine)

useful as aldose reductase inhibitors for treating complications of diabetes and galactosemia.

Summary of Invention

The 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones of the present invention are represented by formula (I):



(I)

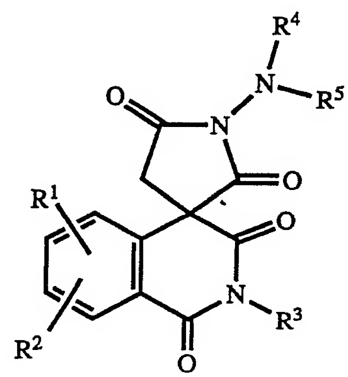
wherein:

R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl (lower alkyl) oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms;

R^3 is lower alkyl containing 1 to 6 carbon atoms, aryl, aryl (lower alkyl) or dihalogen substituted aryl (lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms;

R^4 and R^5 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, aryl or aryl (lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, alkanoyl of 2 to 5 carbon atoms, carboalkoxy, alkylsulfoxy, arylsulfoxy, alkylsulfonyl, trifluoromethylsulfonyl, arylsulfonyl or R^4 and R^5 are joined to form a heterocyclic ring of 5 to 7 ring atoms including the nitrogen atom to which they are joined, and pharmaceutically acceptable salts thereof when R^4 and R^5 are hydrogen, alkyl or aryl.

A more preferred group of compounds of the present invention is represented by formula (II):



(II)

wherein R^1 and R^2 are hydrogen or halogen, R^3 is a dihalogen substituted benzyl, R^4 and R^5 are hydrogen, acyl, carboalkoxy or trifluoromethanesulfonyl.

The most preferred compounds of the present invention are set forth below:

1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]-6-fluorospiro[isoquinoline-4(1H), 3'-pyrrolidine]-1,2',3,5'(2H)-tetrone;

N-[2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]iminodicarbonic acid dimethyl ester;

N-[2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[iso-quinoline-4(1H),3'-pyrrolidin]-1'-yl]acetamide; and

N-[2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[iso-quinoline-4(1H),3'-pyrrolidin]-1'-yl]-1,1,1-trifluoromethanesulfonamide.

The compounds of formula (I) all possess at least one asymmetric carbon atom, namely the spiro carbon atom at position 3' of the pyrrolidine ring. The compounds of formula (I) therefore exist, and may be isolated, in two or more stereoisomeric forms. This invention encompasses the compounds of formula (I) in racemic form or in any optically active form.

The 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones can be prepared by the processes described hereinafter.

A method is provided for preventing or relieving diabetes mellitus associated complications in a diabetic mammal by administering to said mammal a prophylactic or alleviating amount of the compounds of formula (I). Such complications include neuropathy, nephropathy, retinopathy, keratopathy, diabetic uveitis, cataracts and limited joint mobility.

The compounds of formula (I), when admixed with a pharmaceutically acceptable carrier, form a pharmaceutical composition which can be used according to the preceding method.

The 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2'3,5'(2H)-tetrones of this invention may be administered to mammals, for example, man, cattle, or rabbits, either alone or in dosage forms, i.e., capsules or tablets, combined with pharmacologically acceptable excipients.

The compounds of this invention may be given orally. However, the method of administering the present active ingredients of this invention is not to be construed as limited to a particular mode of administration. For example, the compounds may be administered topically directly to the eye in the form of drops of sterile, buffered ophthalmic solutions, preferably of pH 7.2-7.6. Also, they may be administered orally in solid form containing such excipients as starch, milk sugar, certain types of clay and so forth. They may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration, they may be used in the form of a

sterile solution, preferably of pH 7.2-7.6, containing a pharmaceutically acceptable buffer.

The dosage of the 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'-(2H)-tetrones will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular host under treatment. Generally, treatment is initiated with small dosages substantially less than the optimal dose of the compound. Thereafter, the dosage is increased by small increments until efficacy is obtained. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects. For topical administration, a 0.05-1.0% solution may be administered dropwise in the eye. The frequency of instillation varies with the subject under treatment from a drop every two or three days to once daily. For oral or parenteral administration a preferred level of dosage ranges from about 1.0 mg to about 10.0 mg per kilo of body weight per day, although aforementioned variations will occur. However, a dosage level that is in the range of from about 1.0 mg to about 10.0 mg per kilo of body weight per day is most satisfactory.

Unit dosage forms such as capsules, tablets, pills and the like may contain from about 5.0 mg to about 25.0 mg of the active ingredients of this invention with a pharmaceutical carrier. Thus, for oral administration, capsules can contain from between about 5.0 mg to about 25.0 mg of the active ingredients of this invention with or without a pharmaceutical diluent. Tablets, either effervescent or noneffervescent, can contain between about 5.0 to 25.0 mg of the active ingredients of this invention together with conventional pharmaceutical carriers. Thus tablets, which may be coated and either effervescent or noneffervescent, may be prepared according to the known art. Inert diluents or carriers, for example, magnesium carbonate or lactose, can be used together with conventional disintegrating agents for example, magnesium stearate.

The 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2'3,5'(2H)-tetrones also can be used in combination with insulin or oral hypoglycemic agents to produce a beneficial effect in the treatment of diabetes mellitus. In this instance, commercially available insulin preparations or oral hypoglycemic agents, exemplified by acetohexamide, chlorpropamide, tolazamide, tolbutamide and phenformin, are suitable. The compounds hereof can be administered sequentially or simultaneously with insulin or the oral hypoglycemic agent. Suitable methods of administration, compositions and doses of the insulin preparation or oral hypoglycemic agent are described in medical

textbooks; for instance, *Physicians' Desk Reference*, 42 ed., Medical Economics Co., Oradell, N.J., U.S.A., 1988.

The aldose reductase inhibiting property of the compounds of this invention and the utilization of the compounds in preventing, diminishing and alleviating diabetic complications are demonstrable in experiments using galactosemic rats, see Dvornik *et al.*, Science, *182*, 1146 (1973). Such experiments are exemplified hereinbelow after the listing of the following general comments pertaining to these experiments:

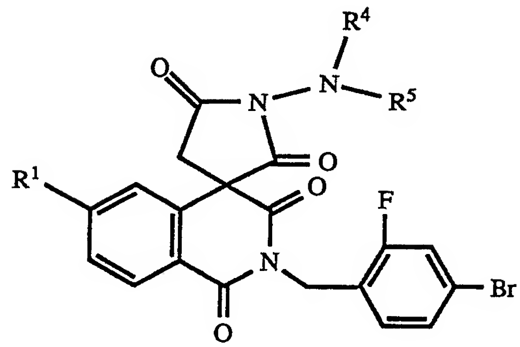
(a) Four or more groups of six male rats, 50-70 g, Sprague-Dawley strain, were used. The first group, the control group, was fed a mixture of laboratory chow (rodent Laboratory Chow, Purina) and glucose at 20% (w/w %) concentration. An untreated galactosemic group was fed a similar diet in which galactose was substituted for glucose. The third group was fed a diet prepared by mixing a given amount of the test compound with the galactose containing diet. The concentration of galactose in the diet of the treated groups was the same as that for the untreated galactosemic group.

(b) After four days, the animals were killed by euthanization. Both the lens and sciatic nerve were removed, weighed and stored frozen for polyol determination.

(c) The polyol determination was performed by a modification of the procedure of M. Kraml and L. Cosyns, Clin. Biochem., *2*, 373 (1969). Only two minor reagent changes were made: (a) the rinsing mixture was an aqueous 5% (w/v) trichloroacetic acid solution and (b) the stock solution was prepared by dissolving 25 mg of dulcitol in 100 mL of an aqueous trichloroacetic acid solution. [N.B.: For each experiment the average value found in the tissue from rats fed the glucose diet was subtracted from the individual values found in the corresponding tissue in galactose-fed rats to obtain the amount of polyol accumulated.] The aldose reductase inhibiting effects of the compounds of formula (I) were also tested by employing an *in vitro* testing procedure similar to that described by S. Hayman and J.H. Kinoshita, J. Biol. Chem., *240,* 877 (1965). In the present case the procedure of Hayman and Kinoshita was modified in that the final chromatography step was omitted in the preparation of the enzyme from bovine lens.

The following tabulated results show that the 1'-aminospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones of this invention show the property that they are active *in vivo* and diminish the accumulation of dulcitol in the lenses, sciatic nerves and diaphragm of rats fed galactose. The figures under L, N, and D represent the percentage decrease of dulcitol accumulation in the tissues of the lens, sciatic nerve, and diaphragm, respectively, for treated rats as compared to untreated rats.

ALDOSE REDUCTASE INHIBITORS



R^1	R^4	R^5	% Inhibition *In Vitro* $10^{-5}M$	Dose mg/kg/day	% Lowering Galactitol Accumulation *In Vivo* %(L)	%(N)	%(D)
H	H	H	5	56	82	72	97
F	H	H	0	50.5	54	75	96
H	H	$COCH_3$	20	57	25	73	90
H	H	SO_2CF_3	0	55	NS	NS	66
H	CO_2CH_3	CO_2CH_3	0	55	NS	50	82

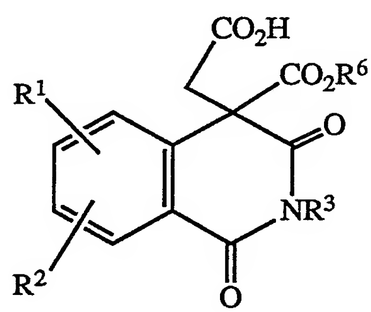
(NS = not significant)

This invention also provides processes for preparing the compounds of formula I or salts thereof. In particular the compounds of formula I may be prepared by one of the following:

a) acylating a compound of formula

$$R^4R^5NNH_2 \qquad \text{(XIII)}$$

wherein R^4 and R^5 are as defined above with a compound of formula



(XIV)

or an activated form thereof

wherein CO_2R^6 is an ester function, e.g. alkyl ester such as the methyl ester, and R^1, R^2 and R^3 are as defined above to give a corresponding compound of formula I and if desired where possible isolating as a salt,

or

b) acylating a compound of formula I wherein one of R^4 and R^5 is hydrogen, the other is selected from hydrogen, lower alkyl, aryl or aryl(loweralkyl)- with an acylating agent (including sulfonylating and sulfinylating agents) containing the group

$$R^8CO\text{-},\ R^8OCO\text{-}\ \text{or}\ R^9S(O)_n\text{-}$$

where R^8 is alkyl and R^9 is alkyl or aryl or, when n is 1, R^9 also represents trifluoromethyl, to give a corresponding compound of formula I wherein R^4 is hydrogen, alkyl, aryl or aryl(loweralkoxy) and R^5 is alkanoyl, carboalkoxy, alkylsulfoxy, arylsulfoxy, alkylsulfonyl, arylsulfonyl or trifluoromethylsulfonyl or R^4 and R^5 are both alkoxycarbonyl, alkanoyl, alkylsulfoxy, arylsulfoxy, alkylsulfonyl, arylsulfonyl or trifluoromethylsulfonyl.

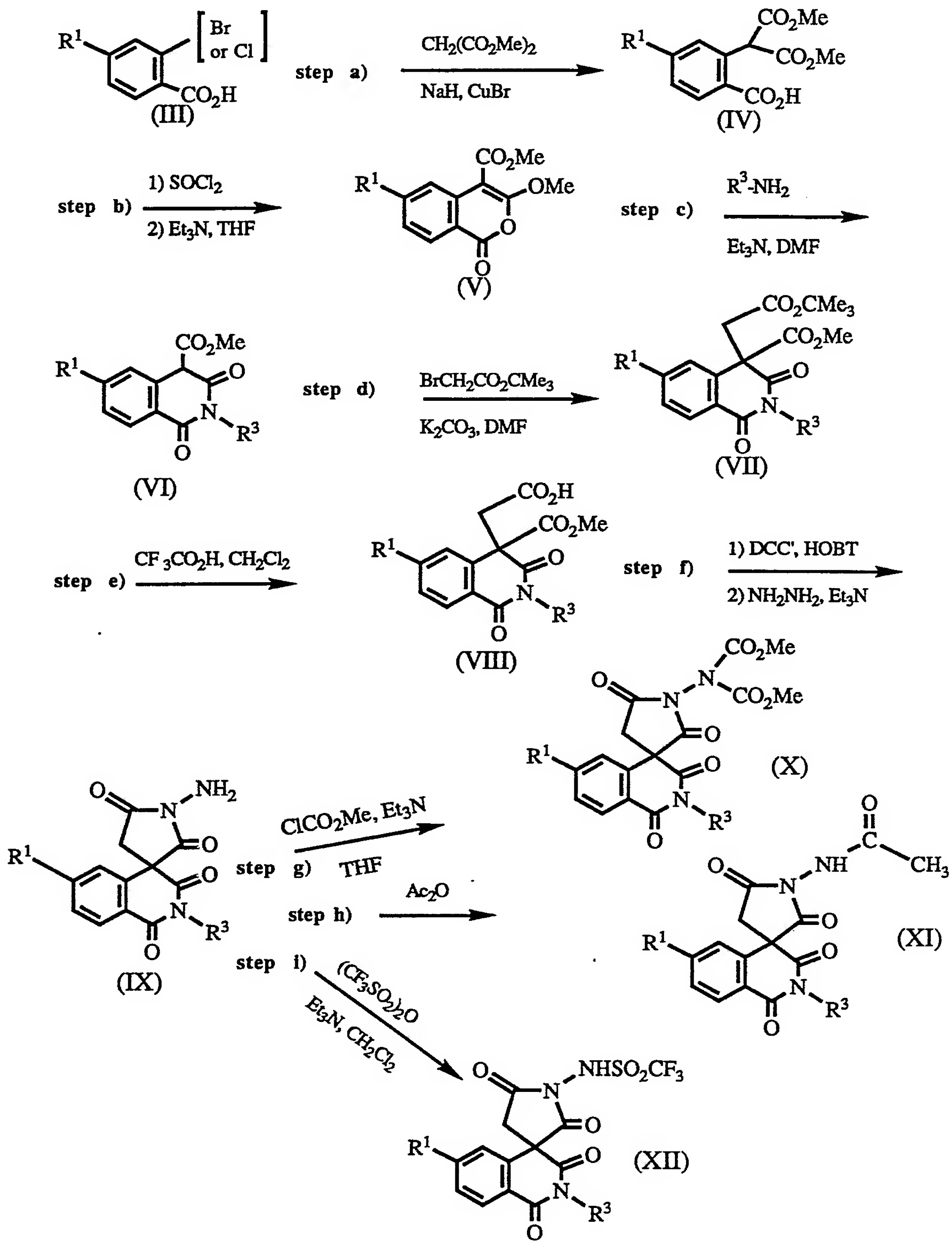
With regard to process a) the acylation may be carried out using the carboxylic acid of formula XIV and a coupling agent such as a carbodiimide e.g. dicyclohexylcarbodiimide. Alternatively the carboxylic acid group may be in activated form e.g. as an acid halide such as the chloride or bromide, or an anhydride such as a mixed anhydride. Processes for preparing compounds of formula III are described in Publication No. GB 2224734 and EP Publication No. 365324

With regard to process b) examples of the acylating agent are acid halides and anhydrides e.g. compounds of formuola R^8COhal, $(R^8CO)_2O$, $R^9S(O)_nhal$, $(R^9SO_2)_2O$ and haloformates such as Cl $COOR^8$.

Multiple acylation may be effected using a stoichiometric excess of acylating agent and more vigorous acylating conditions.

Preferred routes to compounds of the invention are shown in the process below:-

<u>The Process:</u> The 1'-aminospiro[isoq:.inoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrones of the present invention were prepared by the following reaction scheme:



wherein R^1 is halogen or hydrogen and R^3 is a disubstituted aralkyl.

Step a) Reacting either 2-bromobenzoic acid or 2-chlorobenzoic acid of formula (III) wherein R^1 is as defined above with dimethyl malonate and NaH in the presence of a catalytic amount of CuBr to produce the propanedioic acid dimethyl ester of formula (IV) wherein R^1 is as defined above.

The 2-bromobenzoic acids or 2-chlorobenzoic acids of formula (III) required for the present invention are commercially available compounds or can be prepared by known methods.

Step b) The propanedioic acid dimethyl ester of formula (IV) can be reacted with thionyl chloride under refluxing conditions to produce the corresponding acid chloride which upon treatment with Et_3N in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, can produce the compound of formula (V), wherein R^1 is as defined above.

Step c) The compound of formula (V), wherein R^1 is as defined above, is reacted with R^3-NH_2 in the presence of Et_3N in a conventional solvent which does not adversely influence the reaction, for example, DMF, produces the compound of the formula (VI), wherein R^1 and R^3 are as defined above.

Step d) The compound of formula (VI), wherein R^1 and R^3 are as defined above, is reacted with an inorganic base such as potassium carbonate in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide and subsequent addition of the tert-butyl bromoacetate produces the compound of formula (VII), wherein R^1 and R^3 are as defined above.

Step e) The compound of formula (VII), wherein R^1 and R^3 are as defined above, can be reacted with an organic acid such as trifluoroacetic acid in a conventional solvent which does not adversely influence the reaction, for example, methylene chloride, to produce the compound of formula (VIII), wherein R^1 and R^3 are as defined above.

Step f) The compound of formula (VIII), wherein R^1 and R^3 are as defined above, can be reacted with a coupling agent such as 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide (DCC')/1-hydroxybenzotriazole (HOBT) in a conventional solvent which does not adversely influence the reaction, for example, N,N-dimethylformamide, and subsequent addition of hydrazine and Et_3N, produces the compound of formula (IX), wherein R^1 and R^3 are as defined above.

Step g) The compound of formula (IX), wherein R^1 and R^3 are as defined above can be reacted with methyl chloroformate in the presence of Et_3N in a conventional solvent which does not adversely influence the reaction, for example, tetrahydrofuran, to produce the compound of formula (X), wherein R^1 and R^3 are as defined above.

Step h) The compound of formula (IX), wherein R^1 and R^3 are as defined above, can be reacted with acetic anhydride at 70°C, to produce the compound of formula (XI), wherein R^1 and R^3 are as defined above.

Step i) The compound of formula (IX), wherein R^1 and R^3 are as defined above, can be reacted with trifluoromethanesulfonic anhydride in the presence of Et_3N in a conventional solvent which does not adversely influence the reaction, for example, methylene chloride, to produce the compound of formula (XII), wherein R^1 and R^3 are as defined above.

The following examples further illustrate this invention:

EXAMPLE 1

1'-Amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

Step a) (2-Carboxyphenyl)propanedioic Acid Dimethyl Ester

To a rapidly stirred cold suspension (0°C) of 2-bromobenzoic acid (30.0 g, 149.32 mmol), cuprous bromide (2.14 g, 14.93 mmol) and dimethyl malonate (300 mL) was added NaH (80% in mineral oil, 10.75 g, 358.37 mmol) over a 30 minute period, while a stream of dry N_2 was passed over the mixture. After the addition of the NaH had been completed, the mixture was stirred for 10 minutes at room temperature and 30 minutes at 70°C (external oil bath temperature). At this point, the suspension had turned to a solid mass, which was dissolved in H_2O (1000 mL). The aqueous layer was extracted with diethyl ether (3 x 500 mL) and was acidified with HCl (2N). The mixture was extracted with EtOAc and dried over $MgSO_4$. Evaporation gave an

off-white solid which was recrystallized from Et_2O/hexane (after cooling to -20°C) to give a white solid (34.2 g, 90.9%, m.p. 119-120°C).
^1H NMR (DMSO-d_6, 400 MHz): δ 3.67 [s, 6H, -CH($CO_2\underline{CH_3}$)$_2$], 5.72 [s, 1H, -$\underline{CH}$(CO_2CH_3)$_2$], 7.3 (d, J = 7.76 Hz, 1H, Ar-$\underline{H}$), 7.45 (dt, J = 7.66 Hz, 1.12 Hz, 1H, Ar-$\underline{H}$), 7.6 (dt, J = 7.66 Hz, 1.45 Hz, 1H, Ar-$\underline{H}$), 7.94 (dd, J = 7.8 Hz, 1.33 Hz, 1H, Ar-$\underline{H}$), 13.2 (s, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3300-2700 (CO_2H), 1750 (CO), 1730 (CO), 1680 (CO)
MS (m/e): 252 (M^+), 220 (M^+-CH_3OH), 188 (M^+-2 x CH_3OH)
Anal. Calcd.: C, 57.14; H, 4.80
Found: C, 57.05; H; 4.78.

The following compounds were prepared in substantially the same manner as that of Example 1, Step a):

(2-Carboxy-6-fluorophenyl)propanedioic Acid Dimethyl Ester

^1H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, (-$CO_2\underline{Me}$)$_2$], 5.79 [s, 1H, Ar-$\underline{CH}$(CO_2Me)$_2$], 7.12 (dd, J = 10.06 Hz, 2.61 Hz, 1$\underline{H}$, Ar-H), 7.33 (dt, J = 8.48 Hz, 2.64 Hz, 1H, Ar-$\underline{H}$), 8.03 (dd, 8.77 Hz, 6.17 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 3400-2700 (CO_2H), 1730 (CO), 1680 (CO)
MS (m/e): 270 (M^+), 238 (M^+-CH_3OH), 210 (M^+-CH_3OH, -CO), 151 (M^+-CH_3OH, -CO, -CO_2CH_3)
Anal. Calcd.: C, 53.34; H, 4.10
Found: C, 53.36; H, 3.93
m.p. 121.5-123.0°C.

(2-Carboxy-6-chlorophenyl)propanedioic Acid Dimethyl Ester

^1H NMR (DMSO-d_6, 200 MHz): δ 3.69 [s, 6H, (-CO_2Me)$_2$], 5.78 [s, 1H, Ar-CH(CO_2Me)$_2$], 7.38 (d, J = 1.8 Hz, 1H, Ar-$\underline{H}$), 7.58 (dd, J = 7.8 Hz, 1.8 Hz, 1H, Ar-$\underline{H}$), 7.96 (d, J = 8.2 Hz, 1H, Ar-$\underline{H}$), 13.5 (br s, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3200-2700 (CO_2H), 1760 (CO), 1740 (CO), 1690 (CO)
MS (m/e): 286 (20 M^+), 254 (64, M^+-CH_3OH), 222 (60, M^+-2 x CH_3OH)
Anal. Calcd.: C, 50.28; H, 3.87
Found: C, 50.40; H, 3.87
m.p. 125-127°C.

(2-Carboxy-6-bromophenyl)propanedioic Acid Dimethyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.68 [s, 6H, -(CO_2<u>CH_3</u>)$_2$], 5.74 (s, 1H, Ar-<u>CH</u>-), 7.5 (d, J = 2.02 Hz, 1H, Ar-<u>H</u>), 7.70 (dd, J = 8.4 Hz, 1.98 Hz, 1H, Ar-<u>H</u>), 7.87 (d, J = 8.41 Hz, 1H, Ar-<u>H</u>)

IR (KBr, cm^{-1}): 3400-2300 (CO_2H), 1745 (CO), 1720 (CO), 1695 (CO)
MS (m/e): 330 (M^+), 298 (M^+-CH_3OH)
Anal. Calcd.: C, 43.53; H, 3.35
Found: C, 43.56; H, 3.23
m.p. 127-128°C.

Step b) 3-Methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

A mixture of (2-carboxyphenyl)propanedioic acid dimethyl ester (10.0 g, 39.68 mmol) and $SOCl_2$ (100 g) was refluxed for 2 hours. The volatiles were removed *in vacuo* and the crude product (acid chloride) was dissolved in THF (200 mL). Triethylamine (27.64 mL, 198.4 mmol) was added and the mixture was stirred for 30 minutes. The yellowish suspension was poured into HCl (1N, 1000 mL), extracted with EtOAc and the organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/ether/hexane (after cooling to -20°C) gave a white solid (87.6 g, 94.4%, m.p. 129-130°C).

^{1}H NMR (DMSO-d_6, 400 MHz):δ 3.82, (s, 3H, -CO_2<u>Me</u>), 4.03 (s, 3H, -O<u>Me</u>), 7.42 (t, J = 7.26 Hz, 1H, Ar-<u>H</u>), 7.8 (t, J = 8.2 Hz, 1H, Ar-<u>H</u>), 7.9 (d, J = 8.3 Hz, 1H, Ar-<u>H</u>), 8.1 (d, J = 7.26 Hz, 1H, Ar-<u>H</u>)

IR (KBr, cm^{-1}): 1740 (CO), 1685 (CO)
MS (m/e): 234 (15, M^+), 206 (38.5, M^+-CO), 203 (12, M^+-OMe)
Anal. Calcd.: C, 61.59; H. 4.30
Found: C, 61.82; H, 4.29.

The following compounds were prepared in substantially the same manner as that of Example 1, Step b):

6-Fluoro-3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 3.81 (s, 3H, -CO$_2$<u>CH$_3$</u>), 4.06 (s, 3H, -O<u>CH$_3$</u>-), 7.27 (dt, J = 8.3 Hz, 1H, Ar-<u>H</u>), 7.8 (dd, J = 11.83 Hz, 2.49 Hz, 1H, Ar-<u>H</u>), 8.16 (dd, J = 8.92 Hz, 6.2 Hz, 1H, Ar-<u>H</u>)

IR (KBr, cm^{-1}): 1750 (CO), 1685 (CO)
MS (m/e): 252 (24, M$^+$), 224 (54, M$^+$-CO)
Anal. Calcd.: C, 57.15; H, 3.60
Found: C, 57.19; H. 3.57
m.p. 142-143°C.

6-Chloro-3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-D$_6$, 400 MHz): δ 3.81 (s, 3H, -CO$_2$<u>CH$_3$</u>), 4.05 (s, 3H, -O<u>CH$_3$</u>), 7.44 (dd, J = 8.56 Hz, 1.99 Hz, 1H, Ar-<u>H</u>), 8.06 (m, 2H, Ar-<u>H</u>)

IR (KBr, cm^{-1}): 1750 (CO), 1690 (CO)
MS (m/e): 268 (34, M$^+$), 240 (86, M$^+$-CO)
Anal. Calcd.: C, 53.65; H, 3.38
Found: C, 53.59; H, 3.35
m.p. 194-195°C.

6-Bromo-3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 3.81 (s, 3H, -CO$_2$<u>CH$_3$</u>), 4.05 (s, 3H, -O<u>CH$_2$</u>), 7.6 (dd, J = 8.38 Hz, 1.77 Hz, 1H, Ar-<u>H</u>), 8.0 (d, J = 8.39 Hz, 1H, Ar-<u>H</u>), 8.23 (d, J = 1.95 Hz, 1H, Ar-<u>H</u>)

IR (KBr, cm^{-1}): 1740 (CO), 1680 (CO)
MS (m/e): 312 (17 M$^+$), 284 (45, M$^+$-CO)
Anal. Calcd.: C, 46.03; H, 2.90
Found: C, 46.12; H, 2.62
m.p. 200-201°C.

Step c) 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquino-linecarboxylic Acid Methyl Ester

To a solution of 3-methoxy-1-oxo-1H-2-benzopyran-4-carboxylic acid methyl ester (5.0 g, 21.37 mmol) in DMF (100 mL) were added 4-bromo-2-fluorobenzylamine (4.36 g, 21.37 mmol) and Et_3N (5.96 mL, 42.74 mmol). The mixture was stirred at 80°C for 30 minutes, poured into H_2O (1500 mL), acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and crystallization from acetone/hexane (after cooling to -20°C) gave a white solid (7.6 g, 87.7 %, m.p. 149-150°C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ [3.67 (s), 4.0 (s), 3H, -$CO_2\underline{Me}$, tautomeric], [5.06 (q), J = 15.4 Hz, 5.30 (s), 2H, -N$\underline{CH_2}$-, tautomeric], 5.4 (s), 1H, $\underline{CH}$-CO_2Me, tautomeric], 7.07-8.43 (m, 7H, Ar-$\underline{H}$, tautomeric)

IR (KBr, cm^{-1}): 1670 (CC` 1605 (CO)
MS (+ FAB): 406 (80, M^++ H), 374 (40, M^+ -OCH_3)
Anal. Calcd.: C, 53.22; H, 3.23; N, 3.45
Found: C, 53.19; H, 2.98; N, 3.40.

The following compounds were prepared in substantially the same manner as that of Example 1, Step c):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.98 (s, 3H, -$CO_2\underline{CH_3}$), 5.27 (s, 2H, -N$\underline{CH_2}$-), 7.08 (t, J =7.95 Hz, 2H, Ar-$\underline{H}$), 7.2 (m, 1H, Ar-$\underline{H}$), 7.34 (m, 2H, Ar-$\underline{H}$, -$\underline{OH}$), 7.54 (m, 1H, Ar-$\underline{H}$), 8.1-8.26 (m, 2H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 1680 (CO), 1660 (CO), 1610 (CO)
MS (m/e): 423 (M^+), 391 (M^+-CH_3OH)
Anal. Calcd.: C, 50.97; H, 2.85; N, 3.30
Found: C, 50.86; H, 2.86; N, 3.33
m.p. 157-158°C.

6-Chloro-1,2,3,4-tetrahydro-2-methyl-1,3-dioxo-4-isoquinoline-carboxylic Acid Methyl Ester

^{1}H NMR](DMSO-d_6, 200 MHz): δ [3.23 (s), 3.44 (s), tautomeric, 3H, -N<u>CH</u>$_3$], [3.71 (s), 4.03 (s), tautomeric, 3H, -CO_2<u>CH</u>$_3$] , 7.3-8.4 (tautomeric, Ar-<u>H</u>, -OH, 4H)

IR (KBr, cm^{-1}): 3440 (OH), 1680 (CO), 1600 (CO)
MS (m/e): 267 (M^+), 235 (M^+ -OMe)
Anal. Calcd.: C, 53.85; H, 3.77; N, 5.23
Found: C, 53.66; H, 3.63; N, 5.14
m.p. 166-167°C.

6-Bromo-1,2,3,4-tetrahydro-2-methyl-1,3-dioxo-4-isoquinoline-carboxylic Acid Methyl Ester

^{1}H NMR (DMSO-d_6, 400 MHz): δ [3.2 (s), 3.42 (s), 3H, tautomeric, N-<u>CH</u>$_3$], [3.7 (s), 4.01 (s), 3H, tautomeric, -CO_2<u>CH</u>$_3$], [5.33 (s), 1H, tautomeric, Ar-<u>CH</u>-], [7.5 (dd), 7.8 (dd), tautomeric, 1H, Ar-<u>H</u>, [8.0 (d), 8.08 (d), tautomeric, 1H, Ar-<u>H</u>], [8.51 (d), 7.63 (d), tautomeric, 1H, Ar-<u>H</u>)

IR (KBr, cm^{-1}): 1665 (CO), 605 (CO)
MS (m/e): 311 (M^+)
Anal. Calcd.: C, 46.18; H, 3.23; N, 4.49
Found: C, 45.83; H, 2.77; N, 4.38
m.p. 190-191°C.

Step d) 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethyl-ethyl Ester

To a suspension of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-1,3-dioxo-4-isoquinolinecarboxylic acid methyl ester (4.79 g, 11.58 mmol), K_2CO_3 (3.19 g, 23.16 mmol) in DMF (100 mL) was added tert-butyl bromoacetate (2.81 mL, 17.37 mmol). After stirring at 75°C for 1 hour, the mixture was poured into H_2O, extracted with EtOAc and dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc 4/1) gave a clear oil (5.69 g, 94.5%).
^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.04 [s, 9H, -C(<u>CH</u>$_3$)$_3$], 3.53 s, 3H, -CO_2<u>CH</u>$_3$), 3.60 [dd, J = 17.7 Hz, 2H, -<u>CH</u>$_2$$CO_2(CH_3)_3$], 5.14 (s, 2H, N<u>CH</u>$_2$-), 7.17 (t, J =

8.25 Hz, 1H, Ar-H), 7.36 (dd, J = 8.36 Hz, 1.75 Hz, 1H, Ar-H), 7.6 (m, 3H, Ar-H), 7.77 (dt, J = 7.2 Hz, 1.27 Hz, 1H, Ar-H), 8.19 (dd, J = 8.25 Hz, 1.54 Hz, 1H, Ar-H)

IR ($CHCl_3$, cm^{-1}): 1720 (CO), 1675 (CO)
MS (m/e): 520 $(M + H)^+$, 464 $[M^+-C(CH_3)_3]$.

The following compounds were prepared in substantially the same manner as that of Example 1, Step d):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.10 (s, 9H, $-CMe_3$), 3.55 (s, 3H, $-CO_2CH_3$), 3.62 (d, J = 17.5 Hz, 1H, $-CH_2CO_2CMe_3$), 3.75 (d, J = 17.5 Hz, 1H, $-CH_2CO_2CMe_3$), 5.15 (s, 2H, $-NCH_2-$), 7.15 (t, J = 8.2 Hz, 1H, Ar-H), 7.35 (d, J = 8.2 Hz, 1H, Ar-H), 7.45-7.70 (m, 3H, Ar-H), 8.38 (dd, J = 8.16 Hz, 5.70 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}): 1750 (CO), 1720 (CO), 1675 (CO)
MS (m/e): 538 $(M + H)^+$, 481 $(M^+ + H-CMe_3)$
Anal. Calcd.: C, 53.55; H, 4.12; N, 2.60
Found: C, 53.49; H, 4.00; N, 2.63.

6-Chloro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-2-methyl-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

^{1}H NMR (DMSO-d_6, 200 MHz): δ 1.06 (s, 9H, $-CO_2CMe_3$), 3.3 (s, 3H, $-NCH_3$), 3.6 (s, 3H, $-CO_2CH_3$), 3.67 (q, J = 17.5 Hz, 2H, $-CH_2CO_2CMe_3$), 7.68 (dd, J = 9.0 Hz, 1.6 Hz, 1H, Ar-H), 7.77 (d, J = 2.0 Hz, 1H, Ar-H), 8.21 (d, J = 8.2 Hz, 1H, Ar-H)

IR (KBr, cm^{-1}): 1740 (CO), 1720 (CO), 1680 (CO)
MS (m/e): 381 (M^+)
Anal. Calcd.: C, 56.82; H, 5.28; N, 3.67
Found: C, 57.00; H, 5.41; N, 3.66
m.p. 135-136°C.

6-Bromo-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-2-methyl-1,3-dioxo-4-isoquinolineacetic Acid 1,1-Dimethylethyl Ester

^{1}H NMR (DMSO-d$_6$, 200 MHz): δ1.05[s,9H,-C($\underline{CH}_3$)$_3$],3.28 (s,3H,-N$\underline{CH}_3$),3.59(s,3H, -$CO_2\underline{CH}_3$), 3.58 (d, J = 17.03 Hz, 1H, -$\underline{CH}_2CO_2$-), 3.67 (d, J = 17.03 Hz, 1H, -$\underline{CH}_2CO_2$-), 7.81 (dd, J = 8.4 Hz, 1.85 Hz, 1H, Ar-$\underline{H}$), 7.88 (d, J = 1.81 Hz, 1H, Ar-$\underline{H}$), 8.08 (d, J = 8.4 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 1740 (CO), 1710 (CO), 1670 (CO)
MS (m/e): 425 (M$^+$), 370 (M$^+$ -C_4H_7), 352 (M$^+$-C_4H_9O)
Anal. Calcd.: AC, 50.72; H, 4.73; N, 3.29
Found: C, 50.47; H, 4.68; N, 3.12
m.p. 152-153°C.

Step e) 2-[(4-Bromo-2-fluorophenyl)methyl]-1,2,3,4,-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic Acid

A mixture of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid 1,1-dimethylethyl ester (5.19 g, 9.81 mmol), CH_2Cl_2 (100 mL) and CF_3CO_2H (20 mL) was stirred at room temperature for 5 hours. The volatiles were removed in vacuo and the residue was purified by flash chromatography on acid washed silica gel (5% H_3PO_4 in MeOH), to give a white solid (4.12 g, 90.5%, m.p. 139-140°C).

^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 3.54 (s, 3H, $CO_2\underline{CH}_3$), 3.64 (q, J = 17.67 Hz, 2H, $\underline{CH}_2CO_2H$), 5.12 (q, J = 15.34 Hz, 2H, -N$\underline{CH}_2$-), 7.14 (t, J = 8.22 Hz, 1H, Ar-$\underline{H}$), 7.3 (d, J = 8.3 Hz, 1H, Ar-$\underline{H}$), 7.5-7.6 (m, 3H, Ar-$\underline{H}$), 7.76 (d, J = 7.4 Hz, 1H, Ar-$\underline{H}$), 8.16 (d, J = 7.8 Hz, 1H, Ar-$\underline{H}$), 12.35 (s, 1H, -$CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3280 (OH), 3200-2700 (CO_2H), 1750 (CO), 1720 (CO), 1675 (CO)
MS (m/e): 463 (M$^+$), 445 (M$^+$-H, -OH)
Anal. Calcd.: C, 51.28; H, 3.30; N, 2.99
Found: C, 51.26; H, 3.48; N, 2.95.

The following compound was obtained in substantially the same manner as that of Example 1, Step e):

2-[(4-Bromo-2-fluorophenyl)methyl]-6-fluoro-1,2,3,4-tetrahydro-4-(methoxy- carbonyl)-1,3-dioxo-4-isoquinolineacetic Acid

^1H NMR (DMSO-d_6, 400 MHz): δ 3.56 (s, 3H, $-CO_2\underline{CH_3}$),3.6(d,J = 17.9 Hz, 1H, $-\underline{CH_2}CO_2H$), 3.8 (d, J = 17.9 Hz, 1H, $-\underline{CH_2}CO_2H$), 5.1 (dd, J = 15.5 Hz, 2H, $-N\underline{CH_2}-$), 7.12 (s, J = 8.23 Hz, 1H, Ar-$\underline{H}$), 7.31 (dd, J = 8.28 Hz, 1.68 Hz, 1H, Ar-$\underline{H}$), 7.45 (dt, J = 8.56 Hz, 2.5 Hz, 1H, Ar-$\underline{H}$), 7.54 (dd, J = 9.77 Hz, 1.89 Hz, 1H, Ar-$\underline{H}$), 7.64 (dd, J = 9.61 Hz, 2.46 Hz, 1H, Ar-$\underline{H}$), 8.23 (dd, J = 8.79 Hz, 5.81 Hz, 1H, Ar-$\underline{H}$), 12.67 (br s, 1H, $-CO_2\underline{H}$)

IR (KBr, cm^{-1}): 3400-2700 (CO_2H), 1745 (CO), 1710 (CO), 1670 (CO)
MS (m/e): 481 (M^+), 405 (M^+-CO_2, $-CH_3OH$)
Anal. Calcd.: C, 49.81; H, 2.93; N, 2.90
Found: C, 49.94; H, 3.03; N, 2.84
m.p. 132-133.5°C.

6-Chloro-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-2-methyl-1,3-dioxo-4-isoquinolineacetic Acid

^1H NMR (DMSO-d_6, 200 MHz): δ 3.27 (s, 3H, $-\underline{CH_3}$), 3.59 (s, 3H, $-CO_2\underline{CH_3}$), 3.64 (q, J = 17.5 Hz, 2H, $-\underline{CH_2}CO_2H$), 7.65 (dd, J = 8.6 Hz, 2.0 Hz, 1H, Ar-$\underline{H}$), 7.78 (d, J = 2.0 Hz, 1H, Ar-$\underline{H}$), 8.18 (d, J = 8.0 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 3440 (OH), 3200-2700 (CO_2H), 1750 (CO), 1710 (CO), 1675 (CO)
MS (m/e): 325 (M^+)
Anal. Calcd.: C, 51.63; H, 3.71; N, 4.30
Found: C, 51.73; H, 2.70; N, 4.28
m.p. 195-196°C.

6-Bromo-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-2-methyl-1,3-dioxo-4-isoquinolineacetic Acid

^1H NMR (DMSO-d_6, 200 MHz): δ 3.26 (s, 3H, N-$\underline{CH_3}$), 3.53 (d, J = 17.2 Hz, 1H, $-\underline{CH_2}H$), 3.58 (s, 3H, $-CO_2\underline{CH_3}$), 3.74 (d, J = 17.2 Hz, 1H, $-\underline{CH_2}CO_2H$), 7.77 (dd,

J = 8.2 Hz, 2.2 Hz, 1H, Ar-H), 7.87 (d, J = 2.2 Hz, 1H, Ar-H), 8.0 (d, J = 8.2 Hz, 1H, Ar-H), 12.64 (s, 1H, $-CO_2H$)

IR (KBr, cm^{-1}): 3450-2600 (CO_2H), 1735 (CO), 1700 (CO), 1660 (CO)
MS (m/e): 369 (M^+), 324 (M^+-CO_2H)
Anal. Calcd.: C, 45.43; H, 3.27; N, 3.78
Found: C, 45.04; H, 3.16; N, 3.62
m.p. 194-195°C.

Step f) 1'-Amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

To a solution of 2-[(4-bromo-2-fluorophenyl)methyl]-1,2,3,4-tetrahydro-4-(methoxycarbonyl)-1,3-dioxo-4-isoquinolineacetic acid (2.5 g, 5.39 mmol) in DMF (60 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (DCC', 1.34 g, 7.0 mmol) and 1-hydroxybenzotriazole hydrate (HOBT, 1.09 g, 8.08 mmol). After stirring for 2 hours, anhydrous hydrazine (0.22 mL, 7.0 mmol) was added dropwise, followed by Et_3N (1.5 mL, 10.77 mmol) addition. The mixture was stirred for 30 minutes, poured into H_2O, neutralized with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography (hexane/EtOAc 1:1) and subsequent crystallization from ether/hexane (after cooling to -20°C) gave a white solid (1.68 g, 70.0%, m.p. 95-97°C).

^1H NMR (DMSO-d_6, 400 MHz): δ 3.33 (d, J = 18.2 Hz, 1H, -HCHCO-), 3.51 (d, J = 18.2 Hz, 1H, -HCHCO-), 5.07 (s, 2H, $-NCH_2-$), 5.23 (s, 2H, $-NH_2$), 7.17 (t, J = 8.3 Hz, 1H, Ar-H), 7.33 (dd, J = 8.3 Hz, 1.7 Hz, 1H, Ar-H), 7.54 (m, 2H, Ar-H), 7.63 (t, J = 8.51 Hz, 1H, Ar-H), 7.79 (dt, J = 8.7 Hz, 1.25 Hz, 1H, Ar-H), 8.18 (dd, J = 7.7 Hz, 1.25 Hz, 1H, Ar-H)

IR (KBr cm^{-1}): 3340 (NH), 1720 (C=O), 1670 (C=O)
MS (m/e): 445(4, M^+)
Anal. Calcd.: C, 51.14; H, 2.94; N, 9.42
Found: C, 51.04; H, 2.94; N, 9.30.

The following compound was prepared in substantially the same manner as that of Example 1, Step f)

1'-Amino-2-[(4-bromo-2-fluorophenyl)methyl]-6-fluorospiro[iso-quinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.42 (q, J = 18.2 Hz, 2H, -$\underline{CH_2}$CO-), 5.05 (s, 2H, -N$\underline{CH_2}$-), 5.18 (s, 2H, -N$\underline{H_2}$), 7.15 (t, J = 8.3 Hz, 1H, Ar-$\underline{H}$), 7.33 (dd, J = 8.1 Hz, 1.66 Hz, 1H, Ar-$\underline{H}$), 7.49 (dt, J = 8.5 Hz, 2.29 Hz, 1H, Ar-$\underline{H}$), 7.55 (dd, J = 9.96 Hz, 1.87 Hz, 1H, Ar-$\underline{H}$), 7.6 (dd, J = 9.75 Hz, 2.49 Hz, 1H, Ar-$\underline{H}$), 8.24 (dd, J = 8.9 Hz, 5.8 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 3350 (NH), 3280 (NH), 1730 (C=O), 1710 (C=O), 1670 (C=O)
MS (m/e): 463 (94 M^+)

Anal. Calcd.: C, 49.16; H, 2.61; N, 9.05
Found: C, 49.19; H, 2.66; N, 8.96
m.p. 232-234°C.

EXAMPLE 2

N-[2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro-[isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]-iminodicarbonic Acid Dimethyl Ester

To a cold (0°C) solution of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro-[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (2.0 g, 4.48 mmol) in THF (50 mL) was added Et_3N (3.12 mL, 22.4 mmol) followed by dropwise addition of methyl chloroformate (1.04 mL, 13.44 mmol). After stirring for 30 minutes, the mixture was poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. The organic extracts were dried over $MgSO_4$. Evaporation and purification by flash chromatography on silica gel (hexane/EtOAc 2:1) gave a white solid (2.1 g, 83.3%, m.p. 214-216°C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.74 (s, 3H,-$CO_2C\underline{H}_3$),3.76 (d, J =18.9 Hz, 1H, -$\underline{H}$CHCO-), 3.81 (d, J = 18.9 Hz, 1H, -HC$\underline{H}$CO-), 3.83 (s, 3H, -$CO_2C\underline{H}_3$), 5.1 (s, 2H, -NC$\underline{H}_2$-), 7.18 (t, J = 8.1 Hz, 1H, Ar-$\underline{H}$), 7.34 (dd, J = 8.3 Hz, 1.87 Hz, 1H, Ar-$\underline{H}$), 7.56 (m, 2H, Ar-$\underline{H}$), 7.68 (t, J = 7.47 Hz, 1H, Ar-$\underline{H}$), 7.86 (dt, J = 7.68 Hz, 1.45 Hz, 1H, Ar-$\underline{H}$), 8.21 (dd, J = 7.88 Hz, 1.25 Hz, 1H, Ar-$\underline{H}$)

IR (KBr, cm^{-1}): 1810 (C=O), 1745 (C=O), 1670 (C=O)
MS (m/e): 561 (50, M^+)
Anal. Calcd.: C, 49.13; H, 3.05; N, 7.47
Found: C, 49.33; H, 3.22; N, 7.26.

EXAMPLE 3

N-[2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetra oxospiro-[isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]acetamide

A mixture of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (2.0 g, 4.48 mmol) and acetic anhydride (20 mL) was stirred at 70°C for 30 minutes. The volatiles were removed <u>in vacuo</u> and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 1:1) to give a white solid (1.91 g, 87.3%, m.p. 219-221°C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.98 (s, 3H, -COC$\underline{H}_3$), 3.5 (d, J = 18.9 Hz, 1H, -$\underline{H}$CHCO-), 3.7 (d, J = 18.9 Hz, 1H, -HC$\underline{H}$CO-), 5.09 (dd, J = 16.2 Hz, 2H, -C$\underline{H}_2$-N), 7.17 (t, J = 8.3 Hz, 1H, Ar-$\underline{H}$), 7.35 (d, J = 7.9 Hz, 1H, Ar-$\underline{H}$), 7.56 (m, 2H, Ar-$\underline{H}$), 7.65 (t, J = 7.68 Hz, 1H, Ar-$\underline{H}$), 7.84 (dt, J = 7.68 Hz, 1.25 Hz, 1H, Ar-$\underline{H}$), 8.17 (dd, J = 7.88 Hz, 1.25 Hz, 1H, Ar-$\underline{H}$), 10.95 (s, 1H, -N$\underline{H}$COCH_3)

IR (KBr, cm^{-1}): 3240 (NH), 1740 (C=O), 1700 (C=O), 1660 (C=O)
MS (m/e): 487 (54 M^+), 387 (100, M^+-CONNHCOCH_3)

Anal. Calcd.: C, 51.66; H, 3.10; N, 8.61
Found: C, 51.46; H, 3.12; N, 8.54.

EXAMPLE 4

N-[2-[(4-Bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro- [isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]-1,1,1-trifluoromethanesulfonamide

To a cold (0°C) solution of 1'-amino-2-[(4-bromo-2-fluorophenyl)methyl]spiro-[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone (2.0 g, 4.48 mmol) in anhydrous CH_2Cl_2 was added Et_3N (3.12 mL, 22.4 mmol), followed by dropwise addition of $(CF_3SO_2)_2O$ (2.26 mL, 13.44 mmol). After stirring for 30 minutes the mixture was poured into H_2O, acidified with HCl (2N) and extracted with EtOAc. Evaporation and purification by flash chromatography, on acid washed silica gel (hexane/EtOAc 1:1) gave a yellow solid (1.1 g, 42.5%, m.p. 98-100°C).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.29 (d, J = 18.5 Hz, 1H, -$\underline{H}$CHCO-), 3.5 (d, J = 18.5 Hz, 1H, -HC$\underline{H}$CO-), 5.07 (s, 2H, -NC$\underline{H}_2$-), 7.18 (t, J = 8.1 Hz, 1H, Ar-$\underline{H}$), 7.32 (dd, J = 8.3 Hz, 1.87 Hz, 1H, Ar-$\underline{H}$), 7.38 d, J = 7.88 Hz, 1H, Ar-$\underline{H}$),7.53 (dd, J = 9.96 Hz, 2.07 Hz, 1H, Ar-$\underline{H}$), 7.62 (t, J = 8.5 Hz, 1H, Ar-$\underline{H}$), 7.78 (dt, J = 7.9 Hz, 1.25 Hz, 1H, Ar-$\underline{H}$), 8.15 (dd, J = 7.9 Hz, 1.25 Hz, 1H, Ar-$\underline{H}$)

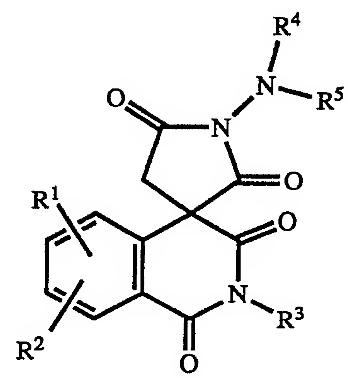
IR (KBr, cm^{-1}): 3400 (NH), 1750 (C=O), 1670 (C=O)
MS (m/e): 577 (94, M^+), 387 (60, M^+ -$CONNHSO_2CF_3$)

Anal. Calcd.: C, 41.54; H, 2.09; N, 7.27
Found: C, 41.20; H, 2.03; N, 7.19.

CLAIMS

We claim:

1. The compounds of structural formula (I)



(I)

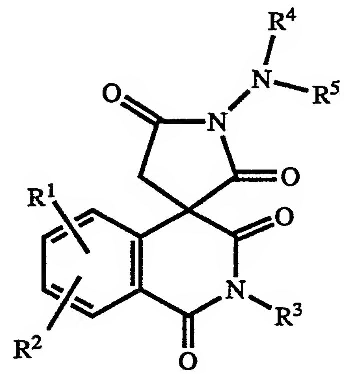
wherein:

R^1 and R^2 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, halogen, lower alkoxy containing 1 to 6 carbon atoms, trifluoromethyl, nitro, aryl or aryl (lower alkyl) oxy wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms;

R^3 is lower alkyl containing 1 to 6 carbon atoms, aryl, aryl (lower alkyl) or dihalogen substituted aryl (lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms;

R^4 and R^5 are independently hydrogen, alkyl containing 1 to 6 carbon atoms, aryl or aryl (lower alkyl) wherein aryl contains 6 to 10 carbon atoms and lower alkyl contains 1 to 6 carbon atoms, acyl, carboalkoxy, alkylsulfoxy, arylsulfoxy, alkylsulfonyl, or arylsulfonyl and the pharmaceutically acceptable salts thereof when R^4 and R^5 are hydrogen, alkyl or aryl.

2. The compounds according to claim 1 of structural formula (II)



(II)

wherein R^1 and R^2 are hydrogen or halogen, R^3 is a dihalogen substituted benzyl, R^4 and R^5 are hydrogen, acyl, carboalkoxy or trifluoromethylsulfonyl.

3. The compound according to claim 2 1'-amino-2-[(4-bromo-2-fluorophenyl)-methyl]spiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

4. The compound according to claim 2 1'-amino-2-[(4-bromo-2-fluorophenyl)-methyl]-6-fluorospiro[isoquinoline-4(1H),3'-pyrrolidine]-1,2',3,5'(2H)-tetrone.

5. The compound according to claim 2 N-[2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]iminodicarbonic acid dimethyl ester.

6. The compound according to claim 2 N-[2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]-acetamide.

7. The compound according to claim 2 N-[2-[(4-bromo-2-fluorophenyl)methyl]-2,3-dihydro-1,2',3,5'-tetraoxospiro[isoquinoline-4(1H),3'-pyrrolidin]-1'-yl]-1,1,1-trifluoromethansulfonamide.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 91/07473

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D471/10; //A61K31/435,(C07D471/10,221:00,209:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category°	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 365 324 (AMERICAN HOME PRODUCTS) 25 April 1990 & US-A-4927831, cited by the applicant see claim 1 ---	1

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 FEBRUARY 1992	24.02.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	ALFARO FAUS I.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9107473 SA 53282

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 05/02/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0365324	25-04-90	US-A-	4927831	22-05-90
		AU-A-	4298389	26-04-90
		GB-A-	2224734	16-05-90
		JP-A-	2164880	25-06-90

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82